REMARKS

Applicant has carefully considered the final Office Action mailed October 13, 2005 and submits the following Amendment and Response in reply thereto. Reconsideration and withdrawal of the outstanding rejections is respectfully requested. Applicant has canceled claims 17-19 and 21-23 solely to expedite prosecution without acquiescing to the grounds of the pending rejections.

Applicant believes that the amendments presented herein place the application in condition for allowance and early notice to that effect is urgently requested.

Status of the Claims

Upon entry of the foregoing amendment, claims 1, 5-8, 10-12, 24, 25 and 42-57 will be pending.

Declaration

The Declaration stands objected to because it claims priority to Provisional Application No. 60/097,864 but Applicant intends to claim priority to Provisional Application No. 60/097,846. Applicant notes that in the Preliminary Amendment filed May 14, 2001, the specification was amended to properly recite the priority claim to Provisional Application No. 60/097,846. To overcome the objection and expedite prosecution, Applicant submits herewith an executed substitute Declaration (Form PTO/SB/01). Withdrawal of the objection is requested.

The Rejection of Claims 1, 5, 34 and 38 under 35 U.S.C. § 102(b)

Applicant acknowledges, with appreciation, the withdrawal of the rejection of claims 1, 5, 34 and 38 as allegedly being anticipated by U.S. Patent No. 5,437,291.

The Rejection of Claims 17-19 and 21-23 under 35 U.S.C. § 112 First Paragraph

Claims 17-19 and 21-23 stand rejected under 35 U.S.C. § 112, first paragraph, because the claims are alleged to lack written description support in the specification. Without acquiescing to the grounds of the rejection and solely to expedite prosecution, Applicants have canceled claims 17-19 and 21-23. The rejection is therefore moot. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 1, 5-8, 24, 25, 42, 43 and 46-57 under 35 U.S.C. § 112 First Paragraph

Claims 1, 5-8, 24, 25, 42, 43 and 46-57 stand rejected under 35 U.S.C. § 112, first paragraph, because it is alleged that the specification does not enable a method of reducing inflammation without causing muscle weakness. Applicant respectfully traverses the rejection because: (1) the Office has not met its burden of establishing a *prima facie* case of lack of enablement because four of the eight Wands factors have not been addressed by the Office; (2) no experimentation would be required to practice the claimed invention and the Office bases its determination of lack of enablement on conclusory statements that ignore or discount what is taught in the specification; and (3) the Office has not provided evidence to support its position

that the statements made in the specification should not be accepted. Applicant respectfully asserts that the rejection is therefore improper and should be withdrawn.

The analysis of whether a particular claim is supported by the disclosure in an application is discussed in detail in the MPEP at 2164.01 and 2164.01(a) *et seq*. Before the Office may assert that a claim is not supported by the disclosure in an application, it must conduct a detailed analysis. This analysis requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which posed the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also *United States v. Telectronics, Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.")

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture*

Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

A conclusion of lack of enablement means that, based on the evidence and consideration of all of the factors laid out in *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

As alluded to above, there are many factors that the Office must consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." Eight of these factors ("the Wands factors") include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Importantly, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The

examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands,* 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407.

Thus, the determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. These factual considerations are discussed more fully in MPEP 2164.08: (scope or breadth of the claims), MPEP 2164.05(a): (nature of the invention and state of the prior art), MPEP 2164.05(b): (level of one of ordinary skill), MPEP 2164.03: (level of predictability in the art and amount of direction provided by the inventor), MPEP 2164.02: (the existence of working examples) and MPEP 2164.06: (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

In the instant case, the Office has not conducted or laid out the required analysis and thus fails to make a *prima facie* case of lack of enablement. The Office bases its determination on conclusory statements that ignore or discount what is taught in the specification without any reason. Finally, the Office has not provided one iota of evidence to support the position that the statements made in the specification should not be accepted. Therefore, the determination that the rejected claims are not enabled by the disclosure is improper and should be withdrawn.

The basis for the rejection seems to be that the Office does not accept the statements made in the instant specification and that the claimed method would involve "unpredictable factors." Specifically, the Office states that "the specification simply does not disclose that

muscle weakness was ever measured." Office Action at page 3. While the Office acknowledges that "reduced inflammation was noted" it appears to discount this observation by stating that it was "only as a side effect of treatment for other disorders." Office Action at page 3. The Office also states that "Accordingly, claims drawn to reducing inflammation without causing muscle weakness, assertedly due to a new (and previously unknown) 'bioeffect', must be considered to be inherently unpredictable and requiring some sort of enablement in addition to mere assertion." Office Action at page 3. In its discussion of the examples, the Office states that "For none of these patients [in the examples] was it disclosed that the doses of Botox™ employed were sufficient to reduce inflammation but below that necessary to cause substantial muscle weakness. Indeed, in most of these cases it appears that Botox™ was employed in a method intended to cause muscle weakness and an anti-inflammatory side effect was observed." Office Action at page 3.

Applicants respectfully submit that the specification includes disclosure of the following:

1. Observation of reduced inflammatory response associated with cholinergic urticaria in a patent with facial nerve disease (page 10 case I, second paragraph, See also Figure 1 showing an anti-inflammatory effect);
2. Observation of reduced inflammatory response in a normal patient without known movement disease (page 11, case II, Figure 2 showing an anti-inflammatory effect);
3. Application to a patient with severe blepharitis-conjunctivitis not responsive to standard anti-inflammatory responses (page 15, second paragraph under "Allergic Blepharoconjunctivitis");

4. Application to a group of patients with blepharitis-conjunctivitis with repeated evidence of benefit (page 15, first paragraph); and
5. Establishment of an animal model which approximates human clinical disease in which evidence of reduced inflammation was observed both by direct observation of signs and patterns of animal behavior (pages 13-14, See also Figure 4 showing anti-inflammatory effect in animal model).

With respect to weakness, the total doses used to treat blepharoconjunctivitis are below that necessary to cause weakness or eyelid closure. See Figure 6. Doses used achieving efficacy for signs of inflammation on the cutaneous examination of the necks of cervical dystonia patients are below the dose range to treat torticolis-cervical dystonia. Page 19, line 4 cites these doses as being between 0.6-15 units which are substantially lower than the dose effective for the treatment of cervical dystonia. Doses used at point injections on the forehead are 2.5 units (page 10, third paragraph).

Throughout the specification applicants teach:

1. Agents for therapy (e.g. Botulinum neurotoxin);
2. Locations and doses for injection;
3. Diagnosis based on nosologic entity (name of disease) for example, blepharo-conjunctivitis; and
4. Expected outcome – e.g. reduced irritation and inflammation.

Applicants teach the dosing range both in the cases of blepharoconjunctivitis and other conditions in human patients and provide experimental data in the allergic guinea pig model.

The doses used were below the doses effective for the treatment of eyelid movement disorders. In cervical injections, the doses used to treat erythematous spot were far below that used to treat involuntary movement diseases.

As stated above, the Office has not set forth a *prima facie* case of lack of enablement because it has not conducted the required analysis of each of the Wands factors.

The Wands Factors

1. Scope or Breadth of the Claims

The first Wands factor requires an analysis of whether or not the enablement provided by the specification is commensurate with the scope of the claims. Claim 1 of the application is representative and it recites:

> 1. A method of reducing inflammation, comprising the step of administering a therapeutically effective dose of a botulinum toxin to an affected area of a subject suffering from inflammation, wherein the botulinum toxin reduces at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce said at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within the affected area.

The Office alleges that "a method of reducing inflammation without causing muscle weakness" is not enabled by the specification. Applicant disagrees because the specification clearly provides enablement for the scope of this claim (as well as all of the claims).

The specification teaches specific doses of botulinum toxin that can be used by a skilled artisan to practice "a method of reducing inflammation without causing muscle weakness." A

skilled artisan would know how to prepare and administer doses of botulinum toxin to practice the invention based on a simple reading of the specification. Any experimentation required to do this would be nothing more than routine.

- On page 19 of the specification, Applicant teaches that "Minimum doses range between 0.6 units to 15 units and are far lower than that required to produce regional weakness."
- On page 3 of the specification, in the Summary of the Invention, Applicant teaches that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammation response."
- On page 4 of the specification, Applicant teaches that "It is a finding of the subject invention that chemodenervative pharmaceuticals such as botulinum toxin in low dosages are effective anti-inflammatory agents. Typical minimum effective doses range from 0.5-5 units as opposed to 20-600 units used for treatment of movement disorders."
- Original claim 2 teaches "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness." Referring back to the specification, the skilled artisan would know what these doses are.

Applicant respectfully asserts that the specification enables the scope of the claimed invention because it teaches how to practice "a method of reducing inflammation without causing muscle weakness." A skilled artisan reading the specification would be informed of the doses of botulinum toxin to use in the claimed methods and would be able to practice the full scope of the invention without undue experimentation.

2. The Nature of the Invention, State of the Prior Art and Level of One of Ordinary Skill

The second, third and fourth Wands factors require an analysis of whether the specification would have been enabling as of the filing date and involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. See MPEP at 2164.05(a). The Office has not addressed these three Wands factors at all in any of its rejections. For this reason alone, Applicant respectfully asserts that no *prima facie* case of non enablement has been made because the Office has not met its burden of conducting the required analysis.

As stated in the MPEP at 2164.01(a): it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the Wands factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands,* 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407. Applicant respectfully asserts that the rejection is improper and should be withdrawn.

3. The Level of Predictability in the Art and Amount of Direction Provided by the Inventor

The fifth and sixth Wands factors require an analysis of the amount of guidance or direction needed to enable the invention and is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. See MPEP at 2164.03. The Office Action concludes, without any analysis, that "claims drawn to reducing inflammation without causing muscle weakness, assertedly due to a new (and previously unknown) 'bioeffect', must be considered to be inherently unpredictable and requiring some sort of enablement in addition to mere assertion." No explanation is given to define what is meant by the term "inherently unpredictable" or why the instant claims fall into this category, newly created by the Office. Applicant respectfully asserts that the claimed methods are not "inherently unpredictable" as alleged by the Office because more than sufficient guidance is provided in the specification to allow a person having ordinary skill in the art to practice the invention. For example, applicants teach observations in patients with diseases, treatment of inflammatory facial disease (blepharoconjunctivitis), treatment of a series of patients with blepharoconjunctivitis, treatment in an animal model. Applicants submit that this is hardly an unpredictable sequence of findings and indicates a high level of predictability.

The guidance provided for practicing the invention may be found throughout the specification. Some of these specific teachings are highlighted above under the discussion of the first Wands factor. The specification teaches the doses required to achieve the claimed effects. As stated in the MPEP at 2164.03, "If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is

predictability in the art." Here, Applicant teaches that "Minimum doses range between 0.6 units to 15 units and are far lower than that required to produce regional weakness." The Office has produced no evidence to suggest that this statement is not true and has provided no reason why it should not be accepted. Withdrawal of the rejection is respectfully requested.

4. The Existence of Working Examples

The MPEP at 2164.02 clearly states that "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." [emphasis added]. The MPEP goes on to say that "An applicant need not have actually reduced the invention to practice prior to filing. *In re Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)." In spite of these clear directives written in the Manual Of Patent Examining Procedure, the Office continues to insist that "the specification simply does not disclose that muscle weakness was ever measured." Office Action at page 3.

In the instant case, even if it were true (which it is not) that no examples were disclosed in the specification, this would not constitute grounds for alleging a lack of enablement because case law and the MPEP make it abundantly clear that examples are simply not required. Furthermore, the absence of examples is not dispositive of whether or not a claimed invention is enabled by the disclosure in a specification. In any event, Applicants respectfully disagree with the allegation that no examples have been provided that support the claimed invention. Applicants point particularly to the example directed to spasmodic torticolis beginning on page 17 of the specification. The Office has provided no reason as to why the examples should be

discounted or why they do not enable the claimed invention. Withdrawal of the rejection is respectfully requested.

5. The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

The last of the Wands factors requires an analysis of the amount of experimentation needed to make or use the invention based on the content of the disclosure.

The Office has not addressed this Wands factor in any of its rejections. For this reason alone, Applicant respectfully asserts that no *prima facie* case of non enablement has been made because the Office has not met its burden of conducting the required analysis. The Office has ignored this Wands factor as well as the three factors discussed above.

As stated in the MPEP at 2164.01(a): it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors [the Wands factors] while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands,* 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407. Withdrawal of the rejection is therefore requested.

In any event, Applicant respectfully asserts that no experimentation would be required to practice the claimed invention; and if any experimentation were required, it would be nothing more than routine. Applicant teaches the doses of botulinum toxin required to obtain the desired effects and a person having skill in the art could practice the invention by simply reading the disclosure and following its teachings.

For all of the foregoing reasons, Applicant respectfully asserts that the rejection is improper and should be withdrawn.

The Rejection of Claims 17-19 and 21-23 under 35 U.S.C. § 102(e)

Claims 17-19 and 21-23 stand rejected under 35 U.S.C. § 102(e) for allegedly being anticipated by U.S. Patent No. 6,063,768. Without acquiescing to the grounds of the rejection and solely to expedite prosecution, Applicant has canceled claims 17-19 and 21-23. The rejection is therefore moot. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 10-12, 17-19 and 21-23 under 35 U.S.C. § 103(a)

Claims 10-12, 17-19 and 21-23 stand rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over U.S. Patent No. 6,063,768 in view of the Merck Manual (1992). Without acquiescing to the grounds of the rejection and solely to expedite prosecution, Applicant has canceled claims 17-19 and 21-23. The rejection as it pertains to claims 17-19 and 21-23 is therefore moot. Applicant respectfully traverses the rejection insofar as it may be applied to claims 10-12, which are addressed below.

Claims 10-12 are directed to:

Claim 10 A method for treating allergic blepharoconjunctivitis comprising the step of administering a therapeutically effective dose of a botulinum toxin in a periocular area of a subject suffering from blepharoconjunctivitis, thereby reducing inflammation.

Claim 11 A method for treating classic type 1 hypersensitivity comprising the step of administrating a botulinum toxin to an affected area of a subject suffering from classic type 1 hypersensitivity, thereby reducing inflammation.

Claim 12 The method of Claim 11, wherein the hypersensitivity is hay fever, rhinitis, allergic rhinitis, allergic forms of eczema, urticaria, rheumatoid arthritis, inflammatory bowel disease, or asthma.

In the Office Action mailed July 5, 2001, the Office acknowledges the following deficiencies in the '768 patent:

> The '768 patent differs from the claimed invention in that it does not teach a method of reducing inflammation due to blepharoconjunctivitis, hay fever, rhinitis, or type 1 hypersensitivity. Neither does the '768 patent teach the use of other anti-inflammatory agents comprising steroids or non-steroids. Office Action at page 7.

To cure these deficiencies, the Office alleges that the Merck Manual teaches that blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity are inflammatory disorders amenable to treatment by anti-inflammatory agents. Office Action at page 7.

Applicant respectfully traverses the rejection because the Office has not set forth a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest

all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure (see MPEP at 2142).

Nowhere in any of the references is there any teaching or suggestion of "allergic blepharoconjunctivitis" or "a periocular area". For these reasons alone, the rejection of claim 10 should be withdrawn. Neither are there any teachings in any of the references of "hay fever," "allergic forms of eczema," "urticaria," or "inflammatory bowel disease." Should the Office maintain the instant rejection, Applicant respectfully requests that the Office specifically indicate where in the references cited in the rejection these teachings appear.

The Office Action alleges that "one of ordinary skill in the art would have been motivated to make the said substitutions because blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity are inflammatory disorders amenable to treatment by anti-inflammatory agents, as taught by the Merck Manual, and steroidal and non-steroidal drugs are common anti-inflammatory agents, also taught by the Merck Manual." Office Action at page 7. Applicants respectfully disagree.

As stated above, the Office Action fails to make a *prima facie* case of obviousness because specific limitations recited in the claims are not taught in the references. Neither has the Office indicated where a person having ordinary skill in the art might find a reasonable expectation of success to arrive at the claimed invention. The Office Action simply does not address this. The motivation cited in the Office Action is also deficient because there is no

suggestion anywhere in the references of using botulinum toxin in the methods of claims 10-12. Applicant respectfully requests that the rejection be withdrawn.

The Rejection of Claim 19 under 35 U.S.C. § 112 First Paragraph

Claim 19 stands rejected under 35 U.S.C. § 112, first paragraph, because the claim is alleged to lack written description support in the specification. Without acquiescing to the grounds of the rejection and solely to expedite prosecution, Applicant has canceled claim 19. The rejection is therefore moot. Withdrawal of the rejection is respectfully requested.

NEW GROUNDS OF REJECTION

The Rejection of Claims 1, 5-8, 10-12, 17-19 and 21-25 under 35 U.S.C. § 112 First Paragraph

Claims 1, 5-8, 10-12, 17-19, 21-25 and 42-57 stand rejected under 35 U.S.C. § 112, first paragraph, because the claims are alleged to lack written description support in the specification. Without acquiescing to the grounds of the rejection and solely to expedite prosecution, Applicant has canceled claims 17-19 and 21-23. The rejection with respect to claims 17-19 and 21-23 is therefore moot.

Applicant submits that the claims are fully described throughout the specification and claims as originally filed including, but not limited to the following:

Claim 1 recites:

1. A method of reducing inflammation, comprising the step of administering a therapeutically effective dose of a botulinum toxin to an affected area of a subject suffering from inflammation, wherein the botulinum toxin reduces at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce said at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within the affected area.

- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."
- On page 19 of the specification, Applicant teaches that "Minimum doses range between 0.6 units to 15 units and are far lower than that required to produce regional weakness."
- On page 3 of the specification, in the Summary of the Invention, Applicant teaches that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammation response."
- On page 4 of the specification, Applicant teaches that "It is a finding of the subject invention that chemodenervative pharmaceuticals such as botulinum toxin in low dosages are effective anti-inflammatory agents. Typical minimum

effective doses range from 0.5-5 units as opposed to 20-600 units used for treatment of movement disorders."

Withdrawal of the rejection is respectfully requested.

Claim 10 recites:

> 10. A method for treating allergic blepharoconjunctivitis comprising the step of administering a therapeutically effective dose of a botulinum toxin in a periocular area of a subject suffering from blepharoconjunctivitis, thereby reducing inflammation.

- Originally filed claim 10 recites: "A method for treating allergic blepharoconjunctivitis comprising the step of injecting a chemodenervating agent in the periocular area."
- On page 7 of the specification, Applicant teaches that "Although botulinum toxin Type A is the currently preferred chemodenervating agent, other immunotypes of botulinum toxin Type B-G may be substituted based on demonstrated anti-inflammatory efficacy."
- On page 15 of the specification, Applicant teaches "Allergic Blepharoconjunctivitis" and the treatment of four patients with botulinum toxin.
- On page 20 of the specification, Applicant discloses that "The fundamental clinical properties associated with and characterizing inflammation are 1. pain or altered sensation 2. erythema 3. edema 4. heat 5. muscular reactivity (often spasm)."

- Applicant also discloses on page 20 that "In patients having...allergic blepharoconjunctivitis, there has been: 1. Repeated improvement in erythema within the denervation filed 2. Improvement in sensation, pain and or itching within the denervation field 3. Improvement in edema formation within the denervation field 4. Differential in apparent heat release within the denervation field 5. Relaxation of human muscle spasms within the denervation field."
- Results of a treated patient with blepharoconjunctivitis is depicted in Figure 6.
- Results of an animal model of allergic blepharoconjunctivitis is given in Figures 3-5.
- 4 patients receiving beneficial results with allergic blepharoconjunctivitis are described on page 15.

Withdrawal of the rejection is respectfully requested.

Claim 11 recites:

> 11. A method for treating classic type 1 hypersensitivity comprising the step of administrating a botulinum toxin to an affected area of a subject suffering from classic type 1 hypersensitivity, thereby reducing inflammation.

- Original claim 11 recites "A method for treating classic type 1 hypersensitivity, comprising the step of administering a chemodenervating agent to the affected area."
- On page 5 of the specification, Applicant discloses that "The subject anti-inflammatory agent's unique property relates to suppression of the component for

the inflammatory response which occurs rapidly, and which is mediated by neural reflex mechanisms. It has been found that Type 1 hypersensitivity reactions are reduced with the subject anti-inflammatory agent. Such hypersensitivity reactions are classic for rapid expression of the inflammatory response often leading to edema with increased vascular permeability, erythema, abnormal sensory experiences, and increased heat release."

- On page 20 of the specification, Applicant discloses that "The fundamental clinical properties associated with and characterizing inflammation are 1. pain or altered sensation 2. erythema 3. edema 4. heat 5. muscular reactivity (often spasm)."
- Applicant also discloses on page 20 that "In patients having...Type 1 hypersensitivity... there has been: 1. Repeated improvement in erythema within the denervation filed 2. Improvement in sensation, pain and or itching within the denervation field 3. Improvement in edema formation within the denervation field 4. Differential in apparent heat release within the denervation field 5. Relaxation of human muscle spasms within the denervation field."
- Then Guinea pig animal model presented in a classic example of type 1 hypersnsitivity (IgE mediated with rapid inflammatory responses). This is clearly demonstrated in experiments and references on the experimental model used.

Withdrawal of the rejection is respectfully requested.

Claim 12 recites:

> 12. The method of Claim 11, wherein the hypersensitivity is hay fever, rhinitis, allergic rhinitis, allergic forms of eczema, urticaria, rheumatoid arthritis, inflammatory bowel disease, or asthma.

- Original claim 12 recites "The method of claim 11, wherein the hypersensitivity includes hay fever and rhinitis."
- The Guinea pig animal model used measures allergic hypersensitivity in eye and nasal passages (see Figures 3-5).
- On page 6 of the specification, Applicant discloses that "It will be appreciated that mast cells are known to contain a number of substances important to inflammatory responses in hypersensitivity reactions, and substantially participate in more generalized inflammatory reactions. The mast cell is abundantly found in pathologic tissue specimens in patients with rheumatoid arthritis, inflammatory bowel disease, certain forms of ocular uveitis, eczema, and asthma."
- Page 10 of the specification describes the treatment of a patient with urticaria using botulinum toxin.
- Page 11 of the specification discloses that "Urticaria refers to the formation of hives occurring usually in response to allergic reactions to pollens, foods, dander or other forms of antigens."
- Page 12 of the specification discloses that "Mast cells are closely associated with Type I hypersensitivity reactions."

- Page 12 of the specification discloses that "Mast cells reactivity has been associated with hayfever blepharoconjunctivitis, asthma, allergic rhinitis, and allergic forms of eczema."

Withdrawal of the rejection is respectfully requested.

Claim 24 recites:

> 24. A method for treating inflammation, comprising the step of administering a botulinum toxin to an affected area of a subject suffering from inflammation in a therapeutically effective dose sufficient to reduce a rapid-phase inflammatory response under neural regulation, thereby reducing at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce the at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within said affected area.

- On page 7 of the specification, Applicant discloses that "Thus, the subject denervating agent, e.g. botulinum toxin, is demonstrated to achieve a reduction in rapid phase inflammatory responses. The responses are under neural regulation, involving mast cells degranulating autocoid releases activated by either non-immunologic or immunologic-based processes."
- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."

- On page 19 of the specification, Applicant teaches that "Minimum doses range between 0.6 units to 15 units and are far lower than that required to produce regional weakness."
- On page 3 of the specification, in the Summary of the Invention, Applicant teaches that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammation response."
- On page 4 of the specification, Applicant teaches that "It is a finding of the subject invention that chemodenervative pharmaceuticals such as botulinum toxin in low dosages are effective anti-inflammatory agents. Typical minimum effective doses range from 0.5-5 units as opposed to 20-600 units used for treatment of movement disorders."

Withdrawal of the rejection is respectfully requested.

The Office alleges that there is no written description support for "the limitations of new claims 42-57 as further limiting of claims 1, 10, 11 and 24. Applicant respectfully disagrees for the following reasons:

Claim 42 recites:

> 42. The method of claim 10, wherein said therapeutically effective dose is sufficient to reduce at least one symptom of

> inflammation but less than a dose necessary to produce substantial muscle weakness within said periocular area.

- Originally filed claim 10 recites: "A method for treating allergic blepharoconjunctivitis comprising the step of injecting a chemodenervating agent in the periocular area."
- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."
- Symptoms of inflammation are cited in the specification on page 20 (pain, erythema, edema, heat). Figures 1-2 depict reduction in edema and erythema. Figures 3-5 depict reduction in edema, erythema and pain in an animal model. Results are discussed on page 14 of the specification.

Withdrawal of the rejection is respectfully requested.

Claim 43 recites:

> 43. The method of claim 11, wherein said therapeutically effective dose is sufficient to reduce at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within said affected area.

- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a

dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."

Withdrawal of the rejection is respectfully requested.

Claim 44 recites:

> 44. The method of claim 10, wherein the chemodenervating agent is selected from the group consisting of botulinum toxins toxin types A, B, C, D, E, F, and G.

- Page 7 of the specification discloses that "Although botulinum toxin Type A is the currently preferred chemodenervating agent, other immunotypes of botulinum toxin Type B-G may be substituted based on demonstrated anti-inflammatory efficacy."

Withdrawal of the rejection is respectfully requested.

Claim 45 recites:

> 45. The method of claim 11, wherein the chemodenervating agent is selected from the group consisting of botulinum toxins toxin types A, B, C, D, E, F, and G.

- Page 7 of the specification discloses that "Although botulinum toxin Type A is the currently preferred chemodenervating agent, other immunotypes of botulinum toxin Type B-G may be substituted based on demonstrated anti-inflammatory efficacy."

Withdrawal of the rejection is respectfully requested.

Claim 46 recites:

> 46. The method of claim 24, wherein said botulinum toxin reduces mast cell degranulation, thereby reducing inflammation.

- Original claim 9 recites "A method for blocking mast cell degranulation, comprising the step of administering a chemodenervating agent to an anatomic region."
- Page 7 of the specification discloses that "the agent works to reduce inflammation by reducing histamine and other preformed mediator releases associated with mast cell degranulation."
- The Guinea pig animal model is useful for measuring mast cell degranulation. Mast cells are abundant in sensitized conjunctiva.

Withdrawal of the rejection is respectfully requested.

Claim 47 recites:

> 47. The method of claim 46, wherein the mast cell is activated by either non-immunologic or immunologic-based processes.

- Page 7 of the specification discloses that "The responses are under neural regulation, involving mast cells degranulating autocoid releases activated by either non-immunologic or immunologic based processes."

Withdrawal of the rejection is respectfully requested.

Claim 48 recites:

> 48. The method of claim 24, wherein the therapeutically effective dose is sufficient to reduce release of preformed mediators of inflammation.

- Page 4 of the specification discloses that "This new bioeffect of anti-inflammatory action is explained by the resultant blockage of mast and nerve cell release of histamine and other preformed mediators which result in vascular dilation, increased permeability, altered sensory experience, edema and erythema. It is thus a finding of this invention that inflammation is inhibited by administration of the subject chemodenervating agent."

Withdrawal of the rejection is respectfully requested.

Claim 49 recites:

> 49. The method of claim 48, wherein the therapeutically effective dose is sufficient to reduce release of leukotrienes, prostaglandins, histamine, serotonin, platelet activating factor, tryptase, or kininogenase.

- Page 7 of the specification discloses that "the agent works to reduce inflammation by reducing histamine and other preformed mediator releases associated with mast cell degranulation."
- Page 6 of the specification discloses that "Mast cell activation has been associated with the production of both preformed mediators such as histamine, newly formed

mediators such as leukotrienes and prostaglandins, cytokines, including interleukin-5, interleukin-8, kininogenase, and platelet activating factor."

- Page 11 of the specification discloses that "The process often involves binding of allergens to the IgE receptor of the mast cell membrane bound IgE, causing release of preformed mediators such as histamine and serotonin as well as newly formed mediators from arachadonic acid such as prostaglandins and leukotrienes, platelet activating factor, kinoginase and tryptase, as well as cytokines."

Withdrawal of the rejection is respectfully requested.

Claim 50 recites:

> 50. The method of claim 1, wherein said inflammation is ocular surface allergic inflammation.

- Page 16 of the specification discloses that "It has now been found that the subject agent has useful anti-inflammatory properties capable of blocking ocular surface allergic inflammation in man and animal models, as well as generalized inflammation within the denervation field created."

Withdrawal of the rejection is respectfully requested.

Claim 51 recites:

> 51. The method of claim 24, wherein the therapeutically effective dose is between one third and several orders of magnitude less than the dose necessary to produce substantial muscle weakness in an affected area.

- Page 3 of the specification discloses that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammatory response."
- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."

Withdrawal of the rejection is respectfully requested.

Claim 52 recites:

> 52. The method of claim 42, wherein the therapeutically effective dose is between one third and several orders of magnitude less than the dose necessary to produce substantial muscle weakness in an affected area.

- Page 3 of the specification discloses that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammatory response."
- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a

dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."

Withdrawal of the rejection is respectfully requested.

Claim 53 recites:

> 53. The method of claim 43, wherein the therapeutically effective dose is between one third and several orders of magnitude less than the dose necessary to produce substantial weakness in an affected area.

- Page 3 of the specification discloses that "It has been found that the use of botulinum toxin in doses from $1/3^{rd}$ to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammatory response."
- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."

Withdrawal of the rejection is respectfully requested.

Claims 54-57 recite:

> 54. The method of claim 1, wherein the at least one symptom of inflammation is heat release, vasodilation, erythema, edema or pain.

55. The method of claim 54, wherein the at least one symptom of inflammation is pain.

56. The method of claim 24, wherein the at least one symptom of inflammation is heat release, vasodilation, erythema, edema or pain.

57. The method of claim 56, wherein the at least one symptom of inflammation is pain.

- Page 20 of the specification discloses that "The fundamental clinical properties associated with and characterizing inflammation are

1. pain or altered sensation
2. erythema (redness)
3. edema
4. heat
5. muscular reactivity (often spasm)

- Page 4 of the specification discloses that "Within this defined area, low dosages of botulinum toxin are demonstrated to block edema, erythema, abnormal sensory experiences, and heat transfer, occurring rapidly over a predefined region."

- Page 8 of the specification discloses "a photograph of the result after three days of injecting a patient suffering from heat release, vasodilation, erythema, and edema with a chemodenervating agent, showing the protective anti-inflammatory effect of the chemodenervating agent, which effect has been noted in less than 24 hours after injection and prior to the development of any weakness, indicating novel dose and pharmacological response for the subject anti-inflammatory bioeffect."

Withdrawal of the rejection is requested.

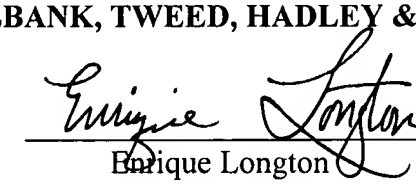
Conclusion

Applicants respectfully request reconsideration and withdrawal of the pending rejections and early allowance of the pending claims. Should the Examiner find that a telephone interview would further prosecution of the application, he is invited to contact the undersigned at his convenience.

The Commissioner is authorized to charge any additional fees associated with this filing, or credit any overpayment, to Deposit Account No. 13-3250. **EXCEPT** for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 13-3250. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with C.F.R. § 1.136(a)(3).

Respectfully submitted,

MILBANK, TWEED, HADLEY & McCLOY LLP

By: 

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